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PHARMACOKINETICS AND METABOLISM OF TEMAZEPAM IN MAN AND SEVERAL ANIMAL SPECIES

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1 Absorption, excretion and detoxification of temazepam were investigated in man, mouse, rat and dog. Considerable interspecies variation was apparent with respect to excretion and metabolite patterns in blood and urine. Animal species were exposed to equal or greater concentrations of all the metabolites occurring in man.

2 Pharmacokinetics of temazepam in man were investigated in a single dose study at two dose levels, and in a multiple dose study. The results of both studies were analyzed and interpreted with the help of compartmental models. Values were obtained for excretion pattern ($0-\infty$), half lives (1.95, 0.5, 10.0 and 1.9 h), amounts in all compartments, and for steady-state conditions.

3 The bioavailability of the hard gelatin capsule dosage form was compared with that of a suspension serving as the ideal dosage form, and found to be acceptable.

Introduction

PHARMACOKINETIC and detoxification studies have been carried out to support the safety and efficacy of temazepam. Studies in animals have been directed toward the validation of toxicity trials, and were concerned with pharmacokinetics and detoxification (Table 1). Studies in man in addition have dealt with first-pass effect, steady-state conditions, elimination rates and accumulation of the parent drug and metabolites, as well as with bioavailability. All the studies involved radio-labelled drug, and tritium-labelled temazepam being used with the label contained in the two 0-positions of the 5-phenyl ring. These positions were chosen because it was assumed that they would be metabolically inert and indeed no tritiated water was found in any of the species investigated.

Absorption and excretion

Absorption and excretion data are summarized in Table 1. Excretion patterns were compared after intravenous and oral doses. There was considerable interspecies variation. In man 80% of the dose was excreted in the urine and 12% in the faeces, whereas in the rat 15% was excreted in the urine and 78% in the faeces. The mouse and dog seemed to be between these extremes, with 37% in the urine and 50-60% in the faeces. In the rat, where most of the excreted drug was found in the faeces, the excretion was mainly biliary and not related to unabsorbed drug. Total recovery was 90% or higher in all four species. In the rat, where biliary excretion was measured, the sum of biliary plus urinary excretion was used for estimating the adsorption. In the mouse, dog and man indirect methods were used. In Table 2 minimal absorption estimates and probable absorption estimates are given, and it can be seen that temazepam was well absorbed — 100% in man and dog, and over 80% in mouse and rat.

Metabolic pathways

The metabolic pathways of temazepam are illustrated in Figure 1. They involved conjugation of the hydroxyl group, loss of the N-methyl, and either conjugation of the desmethyl derivative or demethylation of the *O*-conjugate. All four compounds may be further metabolized to unidentified metabolites. In man, the four compounds shown account for more than 80% of the radioactivity present in blood, and close to 100% of the radioactivity present in urine. It therefore was highly unlikely that an additional major metabolite would be present in man. This finding facilitated the animal work, as only these four compounds could be common to man and animals.

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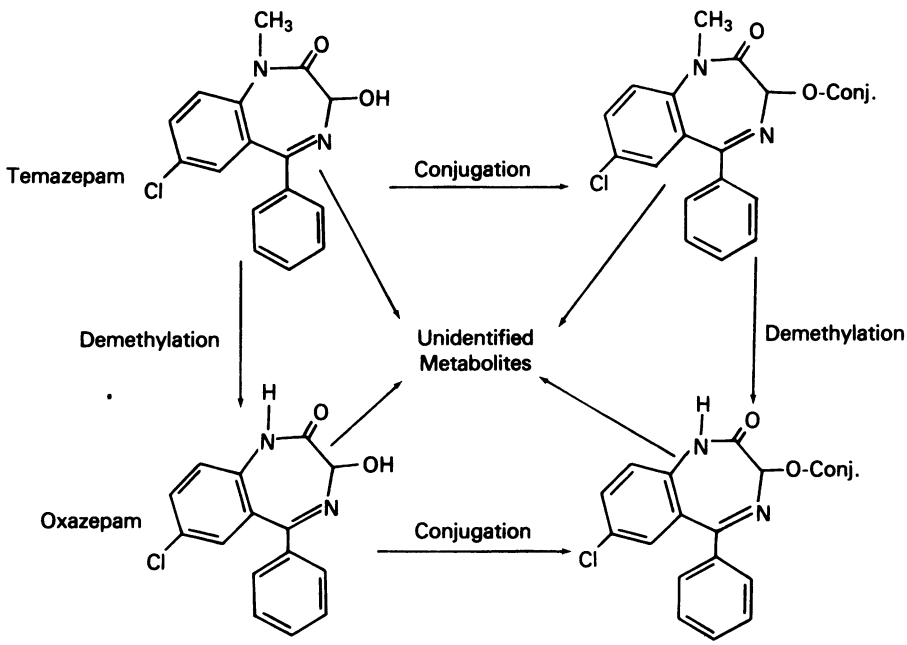

Figure 1 Metabolic pathways of temazepam. Conj., Glucuronate or sulphate.

Detoxification data with blood samples obtained at or near steady-state peak are given in Table 3 as percentage of the radioactivity present in the blood in the left-hand column and as absolute concentrations taking blood level and dose into account in the right-hand column. The four compounds accounted for a large percentage of the radioactivity present in the blood in all the species. However, despite the fact that there were only four compounds, there was considerable interspecies variation. In man, parent drug and its conjugate occurred at high concentrations, and only traces of the N-desmethyl metabolite and its conjugate were found. In the mouse, the N-desmethyl metabolite and its conjugate occurred in high concentrations, and only trace concentrations of the parent drug and its conjugate were found. In the rat, free parent drug and free N-desmethyl metabolite occurred in relatively high concentrations. Their

Table 1 Tabulation of metabolism studies

Species	*Route of Administration*	*Blood Concentrations*	*Pharmacokinetics Tissue Distribution*		*Excretion*	*Detoxification*		
			Normal animals	*Pregnant animals*		*Blood*	*Urine*	*Bile*
Mouse	Oral	XX	X		XX	OX	OX	
	Intravenous	X	X		X	X		X
Rat	Oral	XX	X	OX	XX	XX	XX	X
	Intracardiac	X	X		X	X	X	
	Intravenous	X	X			X		X
Rabbit	Oral	X		OX	X			
Dog	Oral	XX			XX	XX	XX	
	Intravenous	X			X	X		

XX, Single and multiple dose studies; X, Single dose studies only; OX, multiple dose studies only.

conjugates were either not present or present in trace amounts. In the dog, the highest concentration was found for the conjugate of the parent drug, followed by a relatively high concentration of the N-desmethyl metabolite and its conjugate. The parent drug occurred in very low concentrations only. This interspecies variability seemed to create difficulties as far as exposure was concerned. From the right-hand column, it can be seen that because of the very large doses tolerated in the animal species, exposure to the free drug and its conjugate was within about the same range in the animal species as exposure in man. Exposure to the N-desmethyl metabolite and its conjugate was a multiple of that found in man. From these data it can be concluded that at non-toxic doses animal species were exposed to the same or higher concentrations of all the metabolites occurring in man. As no toxicity was found at these dose levels, it means that at a clinically effective dose temazepam is a safe drug in man.

Data for the same four metabolites in urine are given in Table 4 — percentages of the urinary radioactivity and as percentages of the dose. There was a basic difference between the metabolic pattern in the

Table 2 Absorption and excretion of temazepam in man, mouse, rat and dog

Species	Man	Mouse	Rat	Dog
Dose (mg/kg)	0.41	80	80	20
% Dose in urine	79.7	37.3	14.8	37.4
% Dose in faeces	11.9	52.6	77.9	56.8
% Dose in bile	—	—	59.1	—
Total recovery	91.6	89.9	92.8	94.2
Minimum absorption %	80	40	73.9	40
Probable absorption %	100	>80	>80	100

Table 3 Quantities of temazepam and metabolites in blood of man, mouse, rat and dog, at or near the steady-state peak

	Man 0.41 mg/kg/day		*Mouse* 80 mg/kg/day		*Rat* 20 mg/kg/day		*Dog* 20 mg/kg/day	
	% *BRA* *	μg/ml	% *BRA*	μg/ml	% *BRA*	μg/ml	% *BRA*	μg/ml
Temazepam	36.1	0.26	3.9	1.03	21.3	1.07	1.1	0.10
Conjugate temazepam	44.9	0.58	2.2	0.58	2.9	0.14	58.9	5.48
N-desmethyltemazepam	1.8	0.01	48.9	12.91	21.9	1.10	16.1	1.50
Conjugate N-desmethyl-temazepam			22.2	5.86	0.0	0.0	20.1	1.87
Total identified	82.8		77.2		46.1		96.2	
Other metabolites	17.2		22.8		53.9		3.8	

* BRA, percentage of radioactivity present in blood.

Table 4 Quantities of temazepam and metabolites excreted in urine of man, mouse, rat and dog on a multiple dose, once daily regimen (5 days of dosing, 7-8 days of collection)

	Man 0.41 mg/kg/day		*Mouse* 80 mg/kg/day		*Rat* 20 mg/kg/day		*Dog* 20 mg/kg/day	
	% *URA* *	% *Dose*	% *URA*	% *Dose*	% *URA*	% *Dose*	% *URA*	% *Dose*
Total radioactivity	100	81.9	100	35.5	100	14.0	100	42.7
Temazepam	1.8	1.5	0.8	0.3	2.5	0.3	8.6	3.6
Temazepam conjugate(s)	88.3	72.5	7.4	2.6	2.4	0.4	35.1	14.9
N-desmethyltemazepam	1.0	1.0	4.1	1.5	0.6	0.1	8.6	3.7
N-desmethyltemazepam conjugate(s)	7.2	5.8	63.9	22.6	0.8	0.1	36.9	15.8
Total identified	97.3	79.8	76.2	27.0	6.3	0.9	89.2	38.0
Other metabolites	2.7		23.8		93.7		10.8	

* URA, percentage of radioactivity present in urine.

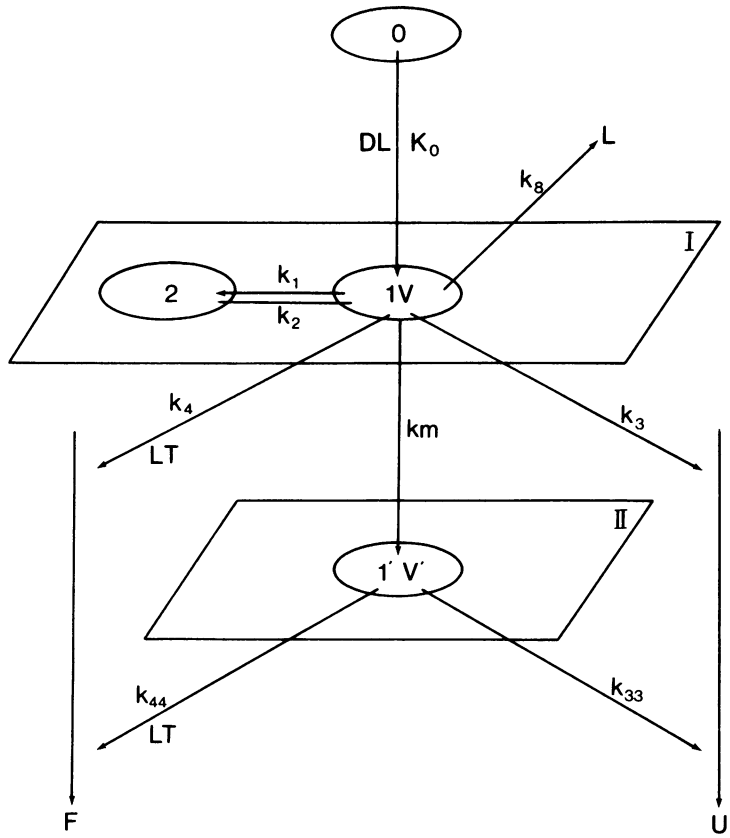

Figure 2 Compartmental model representing the pharmacokinetics of temazepam in man.

blood and the metabolic pattern in the urine. In blood, relative concentrations are measured, in urine absolute amounts are determined. Also, the end-products of the detoxification process are measured in urine. Therefore, the pattern in blood and the pattern in urine do not have to be the same. It is more likely that metabolism had progressed one or more steps further prior to excretion, and this is evident in the results. The high concentrations of parent drug found in the blood of man were not reflected in the urinary excretion. The drug was either conjugated or de-methylated before excretion. The high concentrations of free desmethyl metabolite found in the mouse were also not represented in the urinary excretion. In this case, the metabolite was either conjugated or further metabolized before excretion. In rat again, relatively high concentrations of the free parent drug and the free N-desmethyl metabolite were found in blood. Neither they nor their conjugates appear in more than trace amounts in the urine; additional metabolites of unknown structure were preponderant. The dog was the only species where the metabolite pattern in the blood was maintained in the urine. In man, the four compounds accounted for 97.3% of the radioactivity, and so confirmed the suggestion that no additional major metabolite was present, at least in the urine. Another 13% of the radioactivity was excreted in the faeces. It is known that faecal patterns are not much different from urinary patterns, and so as this was a relatively small percentage of the dose, no further studies were initiated. The concentration of drug and/or metabolites in foetuses and in the pups of lactating animals were also measured. In general, the concentrations were very low, and about a fifth of the concentration in the mothers. It was concluded that the placenta served as a partial barrier.

Pharmacokinetics in man

The pharmacokinetics of temazepam were investigated in two studies. In a single dose study, 15 or 45 mg radiolabelled drug was administered to six human volunteers. In a multiple dose study five

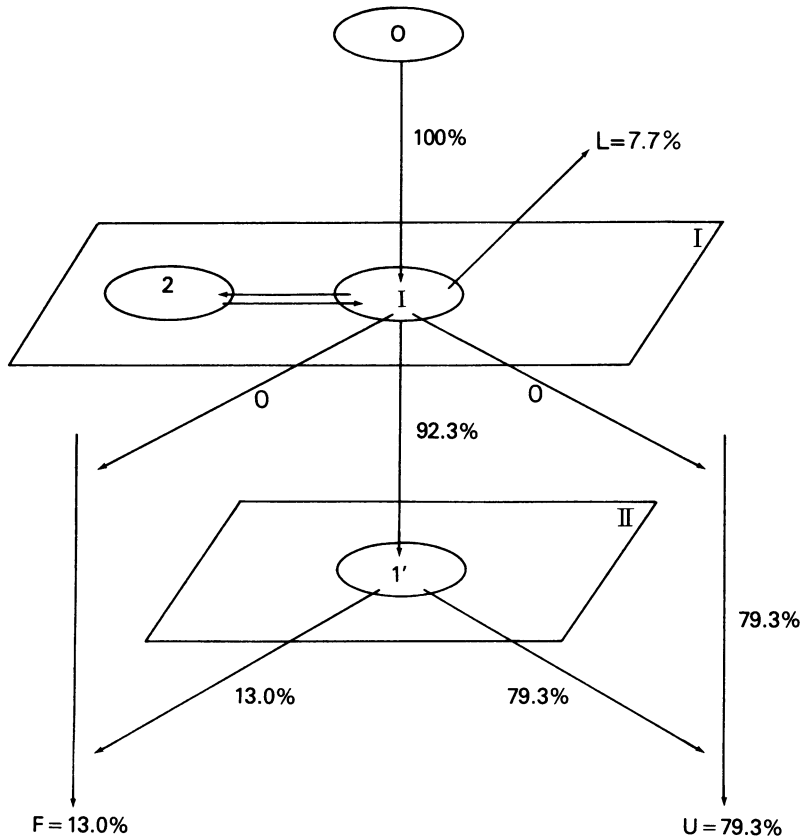

Figure 3 Percentage of radioactivity transferred from $t=0$ to $t=\infty$ (multiple dose).

consecutive doses of 30 mg radiolabelled drug were administered to seven human volunteers. In both studies, blood, urine and faeces were collected. The blood and urine were analyzed for radioactivity and unchanged drug. Faeces were analyzed for radioactivity only. The data from both studies were then analysed and interpreted with the help of a compartmental model. The model chosen had to fulfil certain requirements. Absorption had to be quantitative and to start after a short lag time, the elimination of the unchanged drug had to be biphasic, and both unchanged drug and metabolites had to be excreted into urine and faeces simultaneously. The model fulfilling all these conditions is shown in Figure 2: 100% of the drug was assumed to be in compartment 0 at time 0. After a delay (DL) absorption started, and the drug appeared in the central compartment 1 which was in continuous equilibrium with the peripheral compartment 2. The drug was eliminated from the central compartment by excretion into urine and into faeces or by metabolism. The metabolites in turn were excreted in the urine or faeces.

The data were subjected to simultaneous curve fitting using the equations underlying the model, and a perfect fit was obtained with a correlation of 1. From the mathematical equation the amounts transported along each arrow between zero and time infinity were calculated. The figures obtained are shown in Figure 3. The 100% figure was part of the model. In addition, the loss was 7.7%, with excretion

Table 5 Rate constants and half-lives of temazepam in man

Function	*Parameter* K	$T_{\frac{1}{2}}$
Absorption	0.35	1.95
Elimination of	1.46	0.48
parent drug	0.069	10.0
Elimination of	0.36	1.9
Metabolites		

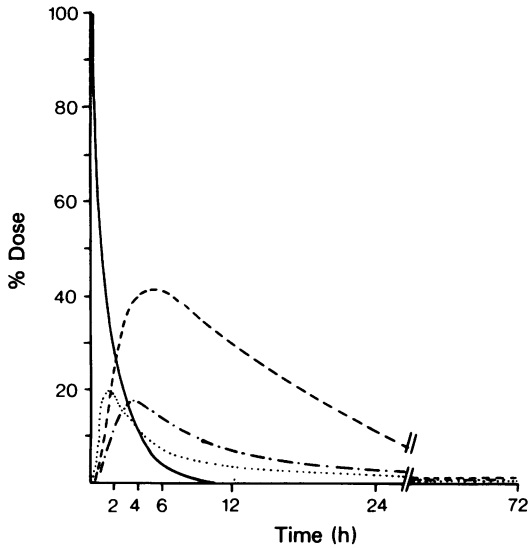

Figure 4 Radioactivity contents of compartments 0, 1, 1′ and 2 following a single oral dose (15 mg/subject) of ^{3}H-temazepam. ————, Compartment 0; — — — —, deep tissue Compartment 2; -------, Compartment 1; —·—·—·, Compartment 1′.

from the central compartment into urine and faeces negligible; 92.3% of the drug was metabolized and of the metabolites, 13% was excreted in the faeces and 79.3% into the urine. The overall rate constants were also calculated (Table 5). The delay time was 24 min and the half-life of absorption was 1.95 hours. The peak was expected to occur 2-3 h after drug administration. The elimination of the parent drug occurred with half-lives of 0.5 and 10 h, and the metabolites were eliminated with a half-life of 1.9 hours. As no parent drug was excreted, the 10 h half-life is interpreted as the half-life of its metabolism. Metabolism of the parent drug was therefore the rate-limiting step in the elimination of temazepam from the systemic circulation. The obvious conclusion from these results was that the metabolites once formed were speedily excreted.

The actual amounts present in each compartment as a function of time are given in Figure 4. The absorption of the drug from the gastrointestinal compartment is shown by the solid curve. It started after a short delay time and was complete after five absorption half-lives or 10 hours. The drug appeared in the central compartment where a peak was achieved at about 2 h — the peak amount being 20% of the dose. Most of the unchanged drug was further distributed to the peripheral compartment. In that

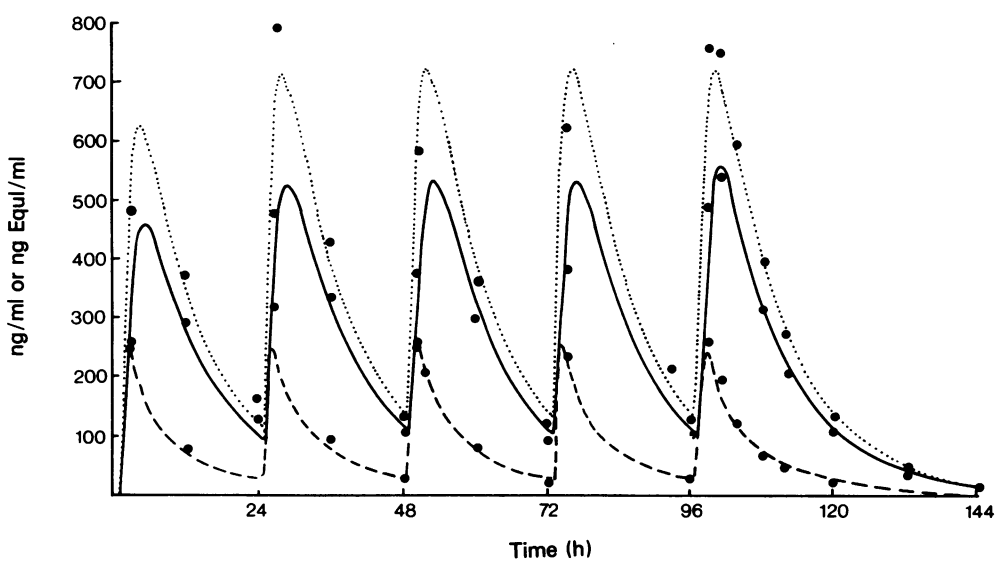

Figure 5 Blood levels of total radioactivity, unchanged temazepam and conjugated material during and following five consecutive doses (30 mg/subject/day) of ^{3}H-temazepam in man. Comparison of calculated curves with observed points. ●, Observed; -------, calculated total radioactivity; ————, calculated conjugated material; — — — —, calculated unchanged temazepam.

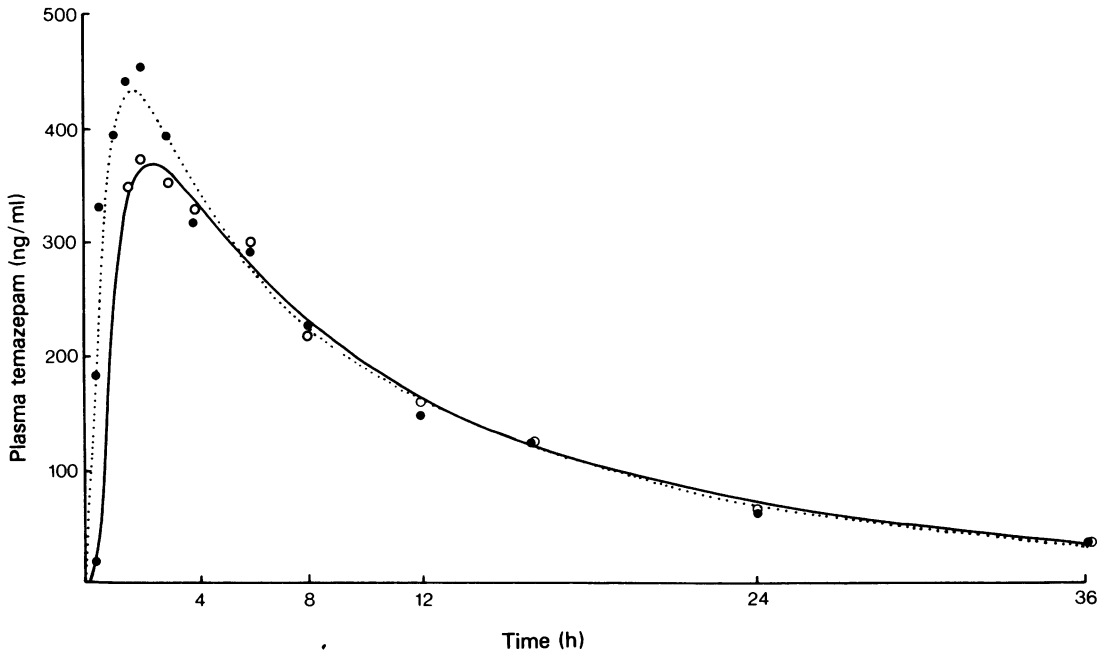

Figure 6 Mean plasma concentrations of temazepam after a single oral dose in human volunteers. Curves obtained by computer fitting of date points. Suspension: . . . . . ., calculated; ●, observed. Capsule: ——, calculated; ○, observed.

compartment, the peak concentration was over 40% and occurred at 6 hours. The emptying of that compartment occurred with a half-life of 10 hours. The metabolites were not accumulated. The highest amount was 18% measured at 4 hours. They also seemed to be eliminated with a half-life of 10 h (Figure 4). However, it should be remembered that 10 h is the half-life of their formation, and once formed, their excretion half-life was only 2 hours. The longest half-life of 10 h is also the rate-determining half-life for attaining steady-state conditions. This is well documented by the multiple dose study (Figure 5). The steady state was attained on the third day for total radioactivity, metabolites or parent drug, and there was little or no accumulation of the parent drug or the metabolites.

Bioavailability

In these studies a hard gelatin capsule was compared with an equipotent suspension in 24 volunteers using a crossover design. The result is shown in Figure 6. The excretion phase of the two formulations was identical. It was biphasic with half-lives of 0.5 and 10 hours. There was a difference in the absorption phase, with the absorption of the suspension starting immediately, and the absorption of the capsule being delayed. The rate of absorption for the suspension was somewhat faster than the rate for the capsules. These differences resulted in a different time to peak and different peak heights. No difference was found with respect to the area under the curve. It is not unusual to find differences in the absorption parameters when comparing a capsule with an equipotent suspension, and it was concluded that as both formulations delivered the same amount of active drug to the systemic circulation, the hard gelatin capsule dosage form was an acceptable formulation.

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